Strategies of assessing and quantifying radiation treatment metabolic tumor response using F18 FDG Positron Emission Tomography (PET)

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Abstract

The use of positron emission tomography (PET) using F18 labeled fluorodeoxyglucose (FDG) for both oncology disease staging and radiation therapy target volume delineation has steadily increased over the last decade, and FDG-PET is today readily available in all major medical centers. The goal of anti tumor treatment, including chemotherapy and/or radiation therapy is to diminish a tumor cell population, ideally to the state of total eradication. Reducing the number of viable tumor cells can lead to a reduction in anatomical tumor size, and may also be correlated with decreased FDG uptake. Efforts to assess tumor response to therapy have attempted to describe and quantify changes in glucose utilization, also referred to as metabolic tumor response. In this review, an attempt is made to present and discuss methodologies to assess and quantify tumor metabolic response to radiation therapy or chemo-radiation treatment courses.

The use of positron emission tomography (PET) using F18 labeled fluorodeoxyglucose (FDG) for both oncology disease staging and radiation therapy target volume delineation has steadily increased over the last decade, and FDG-PET is today readily available in all major medical centers. Both uses take advantage of increased glucose transport and hexokinase levels in tumor cells, resulting in disproportionally high intracellular trapping of FDG-6-phosphate when compared to normal healthy tissues. In malignant tumors, FDG uptake has been shown to be related to both proliferative activity as well as the number of viable cells [1–6]. The goal of anti tumor treatment, including chemotherapy and/or radiation therapy is to diminish a tumor cell population, ideally to the state of total eradication. Reducing the number of viable tumor cells can lead to a reduction in anatomical tumor size, and may also be correlated with decreased FDG uptake. However, tumor response to therapy does not always lead to significant volume reductions assessable by CT and/or MRI. In fact, anatomically stable tumor volume and partial tumor response by trans-sectional imaging create particular challenges in the assessment of the persistence of residual viable tumor. Thus, it comes as no surprise that efforts to assess tumor response to therapy have attempted to describe and quantify changes in glucose utilization, also referred to as metabolic tumor response. An analysis of the National Oncologic PET Registry published in 2008 revealed that 19% of registered scans were acquired for treatment monitoring [7], a number that is certain to increase in coming years.

In this review, an attempt is made to present and discuss methodologies to assess and quantify tumor metabolic response to radiation therapy or chemo-radiation treatment courses. This review appears necessary as a variety of measures to quantify regional tissue glucose metabolism have been established, or recommended. While exemplary published clinical data are referenced in the context of critically assessing quantitative approaches to response assessment, this overview is not intended to comprehensively summarize the available literature.

Quantitative assessment of FDG uptake in tissues

Rationale for quantitative analysis

For both oncology disease staging and response assessment following a therapeutic intervention,
visual assessment of a focus of pathologic uptake, and its reduction or normalization after therapy may arguably suffice. In fact for response assessment for hematological malignancies standardized in the International Harmonization Project in Lymphoma, complete remission is assumed if FDG uptake of lymphomas by visual assessment does not exceed the uptake in the mediastinal blood pool [8]. However, if FDG uptake following treatment is visually reduced, yet still above background metabolic activity, only quantitative analysis will allow to meaningfully assessing the amount of change.

**Standardized uptake value (SUV): Concept and limitations**

The uptake of F18 FDG in tissue can be expressed as an activity concentration value such as Bq/cm³, a value that can be directly derived from the PET image-date. More commonly, FDG uptake is expressed as a standardized uptake value (SUV). SUV is calculated as an index derived from the FDG concentration in a particular tissue divided by the ratio of the injected dose to the subject’s body weight. A PET image can thus be understood as a SUV map, composed of image volume elements (voxels) that each carry a distinct SUV.

Potentially limiting the value of using SUV to quantify FDG uptake is the fact that a particular SUV cannot be understood as a singular objective value, in fact SUV has to be considered a semiquantitative assessment. Any measured SUV is depended on a number of factors, with time after radiolabeled glucose injection and equipment used being the most critical to allow comparison between studies in general, as well as baseline and follow-up studies. Ideally PET imaging of the FDG uptake is acquired when the activity concentration in tissue is linearly correlated with net FDG phosphorylation [9]. In clinical practice this state is often arbitrarily assumed at 50 to 70 minutes after injection. However, in most tumor types changes in SUV (mostly increases) can be measured well beyond this time, making standardized protocols for serial PET measurements to assess a particular change a necessity [10].

Factors such as unrecognized FDG extravasation at the site of injection, and high blood glucose levels in diabetic patients or a postprandial study can lead to erroneous low tumor SUV [11,12]. Other limitations to the use of SUV as a quantitative measure are related to the impact of the subject’s body habit, mainly the ratio of total body fat relative to overall body weight. White body fat participates little in FDG metabolism, creating the possibility of an artificially high tumor and normal organ SUV [13,14]. While this may be predominantly an issue for inter-person comparisons, and less so for serial assessments in the same person, this observation has still potential relevance for intra-individual repeat assessments in the field of oncology, as side effects from therapeutic measures often cause weight loss, and thus body fat loss. Ways to account for body composition and its effects on SUV, is to calculate a SUL (standardized uptake normalized to lean body mass), or normalization to body surface. While SUL is favored by select investigators, SUV remains the most commonly used clinical metric to report uptake of FDG in tissues.

**SUVmax**

In clinical practice, the FDG uptake in a ROI such as a tumor is most often reduced to a single number, the maximum measured SUV value or SUVmax. A tumor SUVmax represents the uptake within a single voxel inside an arbitrary ROI, such as a sphere encompassing a lesion or an automatic threshold rendered volume over the tumor. Often, the “search” for a lesion SUVmax is based on a visual assessment of a maximum intensity projection (MIP) PET reconstruction, as visualized in Figure 1A and B, during which an uptake anomaly is identified. The user then places a sphere of variable size over the ROI to include the grossly abnormal uptake region, and a vendor provided algorithm determines the highest SUV within the selected region (Figure 2A). Different SUVmax can be reported for multiple lesions.

While relatively robust and quick to assess, criticisms of rendering a SUVmax are based on concerns that data noise may affect the accuracy of this maximum uptake reading. In serial assessments, SUVmax values are readily produced as long as post-treatment FDG uptake remains pathologic. Upon reduction or normalization of pathologic FDG uptake in a prior lesion, an anatomically different uptake region that may not represent the treated lesion may be visually selected in error to derive a SUVmax, unless correlation with anatomic computed tomography (CT) imaging is available.

**Peak SUV**

To overcome the limitations of noise issues associated with reporting the SUVmax based on a single voxel, a peakSUV may be generated. The peakSUV represents the mean or average SUV over an area in one imaging slice surrounding the location of the SUVmax. Ideally a circle with a diameter of 10 mm is positioned over the SUVmax (Figure 2B). This means of measuring FDG uptake is favored for prospective clinical assessments by the American College of Radiology Imaging Network (ACRIN). A typical trial to use peakSUV as the primary
outcome measure is ACRIN 6668/RTOG 0235. This prospective clinical trial has the primary purpose to determine the role FDG PET acquired shortly after the end of a course of definitive chemoradiation treatment for locally advanced non-small-cell lung cancer in predicting long-term clinical survival. As with reporting SUVmax, serial assessments are reliable as long as pathologic uptake can be visually assessed. Normalization of uptake within a tumor carries risk for false comparisons, unless registered CT data is used for comparative assessment.

**Volume of tissue encompassed by a SUV threshold**

Most vendor supplied PET imaging processing software platforms allow rendering a ROI or structure based on a user selected absolute SUV threshold or a percentage of maximum SUV (Figure 2C). By placing a cursor inside a target region, all voxels above the selected threshold are rendered as an analysis structure. In oncology applications SUV thresholds higher than 2.5 or 3 are often considered to be representative of tumor metabolic activity. Aside from enabling quantification of a mean SUV within such a threshold region, the volume encompassed by a set SUV threshold may also be valuable for serial assessment. Such threshold derived structures are often exported as DICOM structures into radiation therapy treatment planning software for radiation therapy planning structure generation. Any treatment effect may impact on both the mean SUV and the volume of tissue measuring with a FDG uptake above a chosen threshold, and may as such provide the basis for metabolic response assessment.

**Glucose Metabolic Rate Mapping**

Assessing the kinetic of FDG uptake after injection instead of waiting about one hour to start image acquisition allows calculating a ROI glucose metabolic rate (MRglu), a parameter that is not time dependent and may be more objective than assessing a SUV. MRglu depends on a rate constant for free FDG transport from plasma into tissue, a rate constant for transport of free FDG back into plasma, and a rate constant for phosphorylation of FDG inside of cells. If conducted as a voxel by voxel analysis, an MRglu map can be generated which may again be used to derive structures for analysis or for radiation therapy planning. Challenges to the widespread use of MRglu are based on the fact that the patient will need to lay on the PET scanner table for the entire uptake time (about 60 minutes) in addition to typical diagnostic scan times, and the need for repeated arterial blood glucose sampling. Tumor response to therapy may affect the MRglu, making MRglu an alternate, yet more resource intense and more invasive methodology to assess metabolic tumor response.

**Assessment of metabolic response**

**Dimension of change constituting a metabolic response**

In order to be useful for therapy response assessment, any change in FDG metabolism must be larger than potential physiologic FDG uptake fluctuations within tumor tissues. Those fluctuations have been documented to be typically within an approximate 10% range, when FDG PET scans are repeated within few days without interim therapeutic interventions.
No generally accepted criteria for establishing tumor response to treatment have been established. While a consensus paper based on a 2005 Cancer Imaging Program workshop sponsored by the US National Cancer Institute was issued, the panel of experts also recognized that no agreed upon standard for judging the significance of response based on FDG uptake reduction has been identified [20]. Aside from a visual assessment of PET images, which is highly subjective and discouraged for use in clinical trials, SUVmax are most often used to document treatment response. Arbitrary recommendations include a minimum 20% change in SUVmax, or an absolute change in SUV of at least 0.9 [17]. An objective metabolic response has been proposed in the 1999 EORTC PET response criteria as complete resolution of FDG uptake within tumor volume so that it was indistinguishable from surrounding normal tissues [21] (an example for complete FDG uptake resolution is shown in Figure 3).

Timing of repeat assessment

Unlike metabolic response to chemotherapy, where changes in tumor metabolism may be assessed within days or very few weeks post treatment administration, metabolic tumor repose to radiation therapy appears more delayed, with robust response assessment being feasible after a minimum follow-up of six to eight weeks. It has been recognized that FDG decline measured early after a therapeutic intervention may be smaller than declines assessed at later
time points (example shown in Figure 4) [21,22]. Prospective trials assessing the optimal timing of post radiation therapy treatment response are sparse. Increasingly, early response assessments are conducted during treatment or within few weeks after completion of neoadjuvant treatment courses for rectal and esophageal cancer, often showing decline in metabolic tumor activity, but with residual tumor FDG uptake [10,23,24]. Similar data has been shown for cervical cancer patients undergoing chemoradiation, with a subset of cases showing complete metabolic response already during treatment delivery [25]. Longer delays between baseline assessment and follow-up scans (12 weeks) may help distinguishing between treatment-associated inflammatory response and residual viable tumor tissue.

Protocol and technical considerations for response assessment

Based on the above discussed limitations associated with using SUV as the key clinical parameter to report tissue glucose metabolism, particular attention needs to be paid to assuring that baseline and follow-up studies are acquired in comparable ways, as otherwise, variability associated with image data acquisition protocols may be larger than the treatment effects to be measured. The most critical parameter aside from dose injected and patient preparation is the timing of image data acquisition after F18 FDG injection [10]. Standardized institutional protocols are strongly suggested. In multi-center prospective clinical trials, standardization of image-acquisition parameters and
Proposals for novel metabolic response assessment methods

Deformable registration based voxel to voxel mapping

Advanced means of image fusion allow for deformable registration of follow-up CT and PET data onto a baseline scan and afford serial voxel to voxel mapping of metabolic activity (Figure 3). In serial assessments, multiple time points can be assessed and compared against baseline. Conceptually, this approach is similar to tracking contrast media inflow over time in a ROI in dynamic contrast enhanced CT and MRI studies (DCE CT and DCE MRI). Obviously, while DCE CT and MRI studies are based on an analysis of multiple images acquired in a single session over one anatomical region, serial voxel to voxel mapping of follow-up PET onto baseline PET data is not only complicated by a time delay of weeks or months between image acquisitions, but also needs to compensate for potential anatomical changes as a consequence of interim tumor directed treatment. However, deformable registration of anatomic follow-up CT data of a PET-CT data set onto...
critical discussion, FDG PET is increasingly used for select hematological malignancies. While, despite comes and to stratify treatment selection and intensity, and is now used to prognosticate outcomes specifically. At this point in time, it has become clear that baseline, pretreatment FDG uptake can yield prognostic information for some tumor types but not others. FDG uptake change in response to chemotherapy is often more dramatic and may be assessed at earlier time-points than response to radiation therapy, and is now used to prognosticate outcomes and to stratify treatment selection and intensity for select hematological malignancies. While, despite critical discussion, FDG PET is increasingly used in the process of delineating radiation therapy target volumes [28–33], serial assessment of tumor response following a course of radiation therapy is still in its infancy. Ongoing and future prospective clinical trials need to clarify optimal timing of repeat FDG PET assessment, and a level of metabolic uptake reduction predictive of long-term outcomes for specific tumor types. It is actually likely that optimal timing of response assessment and prognostic level of uptake reduction may differ dramatically for different underlying pathologies. Ablative radiation treatments such as stereotactic treatment approaches in the body may yield more dramatic and earlier metabolic uptake normalization than conventionally fractionated radiation regimens. Concurrent administration of chemotherapy may also result in earlier metabolic tumor response than radiation monotherapy. Aside from correlations with pathologic tumor response, afforded in neoadjuvant treatment concepts, a more standardized approach to assessing metabolic tumor response is warranted. As such, aside from institutional preferences, the NCI consensus guidelines, as well as the recently proposed PERCIST criteria may serve in helping to design future prospective clinical trials.

**PERCIST**

PERCIST, or Positron Emission Response Criteria in Solid Tumors, is a recent proposal to standardize metabolic response assessment to anti-tumor therapy [26]. The rationale to develop such a novel standardized approach to tumor response assessment was based on the finding that the biological or metabolic prediction of tumor response during or at the end of a treatment course may be superior to using anatomical measurements based on the widely accepted Response Evaluation Criteria in Solid Tumors (RECIST, and RECIST 1.1) [27]. Measurement criteria for this proposed method address most criticisms and concerns in quantization of PET images. Wahl and colleagues propose to report a SUL_{peak} in the hottest target region. The volume measured is a sphere of 12 mm diameter, equal to a volume of 1 cm^3, centered on the “hottest” area in a PET scan. For a baseline SUL_{peak} to be considered meaningful, the value reported would need to be 1.5 times the value of a 3 cm diameter right liver lobe SUL + 2SD. Owing to having been proposed most recently, no clinical data have been reported using those criteria.

**Summary**

Undoubtedly, measurement and quantization of tumor glucose metabolism at baseline and in follow-up is an attractive yet incompletely explored aspect of oncology care and radiation oncology follow-up specifically. At this point in time, it has become clear that baseline, pretreatment FDG uptake can yield prognostic information for some tumor types but not others. FDG uptake change in response to chemotherapy is often more dramatic and may be assessed at earlier time-points than response to radiation therapy, and is now used to prognosticate outcomes and to stratify treatment selection and intensity for select hematological malignancies. While, despite critical discussion, FDG PET is increasingly used in the process of delineating radiation therapy target volumes [28–33], serial assessment of tumor response following a course of radiation therapy is still in its infancy. Ongoing and future prospective clinical trials need to clarify optimal timing of repeat FDG PET assessment, and a level of metabolic uptake reduction predictive of long-term outcomes for specific tumor types. It is actually likely that optimal timing of response assessment and prognostic level of uptake reduction may differ dramatically for different underlying pathologies. Ablative radiation treatments such as stereotactic treatment approaches in the body may yield more dramatic and earlier metabolic uptake normalization than conventionally fractionated radiation regimens. Concurrent administration of chemotherapy may also result in earlier metabolic tumor response than radiation monotherapy. Aside from correlations with pathologic tumor response, afforded in neoadjuvant treatment concepts, a more standardized approach to assessing metabolic tumor response is warranted. As such, aside from institutional preferences, the NCI consensus guidelines, as well as the recently proposed PERCIST criteria may serve in helping to design future prospective clinical trials.

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**References**

Quantifying F18FDG PET response to radiation therapy


